UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/511,989	05/25/2005	Jenny P Y Ting	5470-368	4540

20792 7590 12/31/2007
MYERS BIGEL SIBLEY & SAJOVEC
PO BOX 37428
RALEIGH, NC 27627

EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
12/31/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/511,989	TING ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe, Ph.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 October 2007*.

2a)☒ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4,16,20,and 27-56* is/are pending in the application.

4a) Of the above claim(s) *27-54* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *4,16,20,55 and 56* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20051222*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Election/Restrictions

Claims 27-54 remain withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/26/07.

Claim Rejections - 35 USC § 112

Claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claims 55 and 56 require that the CATERPILLER 11.3 polypeptide or fragment inhibit "NF-κB function". Applicant points to various locations of the specification alleged to provide support for these claim limitations. However, NF-κB is a protein, and the limitation "inhibit NF-κB function" implies that the function of the protein is inhibited by CATERPILLER 11.3. The specification discloses that CATERPILLER 11.3 inhibits induction of the NF-κB gene mediated by certain other proteins, e.g. MyD88, and not that CLR11.3 has any direct effect on NF-κB itself, inhibition or otherwise.

This rejection would be overcome by amending the claim to indicate that the CLR11.3 polypeptide or fragment is inhibiting induction of the NF-κB gene mediated by those proteins disclosed in the specification.

Claims 4, 16, and 20 remain rejected and claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 4, 16, and 20 remain rejected and claims 55 and 56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid encoding the polypeptide of SEQ ID NO: 18 or amino acids 1-921 of SEQ ID NO: 20, does not reasonably provide enablement for any other CATERPILLER 11.3 polypeptide or any functional fragment of a CATERPILLER 11.3 polypeptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

While the written description and enablement requirements are separate and generally separable requirements, the instant application fails to meet either requirement for essentially the same reasons. The grounds of rejection set forth in the Office action of 4/23/07 are essentially repeated below with modifications required by the amendments.

The claims are broadly directed to a nucleic acid encoding a functional CATERPILLER 11.3 polypeptide, hereafter CLR11.3, or a "functional fragment" of such a CLR11.3 that

comprises a nucleotide binding domain and/or leucine-rich repeat and/or inhibits NF-κB function. The nucleic acid may encode the amino acid sequence of SEQ ID NO: 18 or 20 or with at least 95% sequence identity to SEQ ID NO: 18 or 20; or the nucleic acid may comprise SEQ ID NOs: 17 or 19, is 95% identical to SEQ ID NO: 19, or a nucleotide sequence that hybridizes to the complement of SEQ ID NO: 17 or 19 under the conditions recited in part (c) of claim 4.

The specification discloses two splicing variants of a human CLR11.3, whose amino acid sequences are set forth in SEQ ID NO: 18 and 20. The specification does not describe any other examples of a CLR11.3 from any other organism or any synthetic variants of human CLR11.3. CLR11.3 is disclosed to comprise at least three distinct domains or regions, an unidentified N-terminal domain, a nucleotide binding domain, and a leucine-rich repeat region. As defined in the specification (page 19, lines 23-25), a "functional fragment" is any fragment that retains at least one biological activity normally associated with CLR11.3. The specification does not, however, describe or list a complete range of biological activities possessed by CLR11.3, although it can be inferred that there are at least several based upon the modular structure of CLR11.3 and its structural relationship to other proteins having a structurally related nucleotide binding domain and/or leucine-rich repeat region. One such example, Monarch-1, interacts with "a host of proteins" (page 23, lines 3-5), and other members of the so-called CATERPILLER family interact with themselves, with nucleotides, and with various proteins, lipids, and/or carbohydrates, the identity of which depends upon the specific member. Although CLR11.3 has a purine nucleotide triphosphate binding domain, it is not clear from Table 1 (pages 83-85) that it binds to either ATP or GTP, as others of this family are predicted to do. Thus, it is clear that at least some of the biological activities of CLR11.3 is expected to possess are the ability to bind

various other molecules, and presumable, some fragments of CLR11.3 may be presumed to have at least some of these activities on their own.

The specification does not describe any "function" of CLR11.3 at the molecular level. The only functional information for CLR11.3 provided in the specification (page 114, lines 1-13) is that overexpression of CLR11.3 in a cell carrying an NF-κB-dependent reporter gene reduces induction of the reporter gene in response to overexpression of MyD88 or NIK, i.e. it appears to have a negative regulatory activity in certain inflammatory signaling pathways. However, the specification does not disclose where specifically in the pathway CLR11.3 acts, or what it does or interacts with at the molecular level to reduce induction of expression from an NF-κB-dependent promoter. It is not clear whether inhibition of MyD88- or NIK-mediated induction of an NF-κB-dependent promoter are the only biological activities of CLR11.3. The specification does not describe a "function" known to be associated with the leucine -rich repeats of CLR11.3. Also, the specification does not disclose what part or parts of CLR11.3 are required for the disclosed activities. With respect to new claims 55 and 56, the specification does not teach that CLR11.3 has the function of inhibiting NF-kB itself, nor does the specification teach any changes in sequence of CLR11.3 that would confer such an activity.

Except for the general effects on induction of NF-kB-mediated expression possessed by the entire human CLR11.3, the specification does not describe the other presumed biological activities or assays to detect the activities, much less "functional fragments" that possess at least one of these unknown activities. Consequently, there is no evidence that Applicant was in possession of any functional fragments of the disclosed human CLR11.3 polypeptide, and

identifying such fragments would require undue experimentation to first identify just what those activities are and then determine what fragments possessed the activities.

While a polypeptide of SEQ ID NO: 18 or amino acids 1-921 of SEQ ID NO: 20 may reasonably be assumed to have an activities characteristic of itself, whatever they may be, any specific variant of these polypeptides cannot be assumed to have such activities given the dearth of descriptive and enabling support in the specification as to what those activities are or how to determine them. For example, if one of skill in the art were provided a nucleic acid molecule encoding a polypeptide differing from SEQ ID NO: 18 by a single amino acid, the specification does not provide any descriptive support that would allow one to envision whether the polypeptide would have the requisite activity, nor does it describe a method enabling one to determine by experimentation whether the encoded polypeptide had all the normal biological activities normally associated with CLR11.3, i.e. one would be unable to determine whether the nucleic acid molecule was embraced by the claims, regardless of whether it was a naturally occurring variant or a man-made variant. One would be unable to determine whether the change would result in a loss of polypeptide function, an alteration of polypeptide function, or would be a neutral or silent change.

The court and the Board have repeatedly held (*Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (CA FC, 1991); *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993); *Fiddes v. Baird*, 30 USPQ2d 1481 (BPAI 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)) that an adequate written description of a nucleic acid requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it, irrespective of the complexity or simplicity of the method; what is required is a

description of the nucleic acid itself. It is not sufficient to define DNA or protein solely by its principal biological property, because disclosure of no more than that, as in the instant case, is simply a wish to know the identity of any DNA or protein with that biological property. Naming a type of material generically known to exist, in the absence of knowledge as to what that material consists of, is not a description of that material. When one is unable to envision the detailed constitution of a complex chemical compound having a particular function, such as a nucleic acid, so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e., until after the nucleic acid has been isolated. Thus, claiming all DNA's that achieve a result without defining what means will do so is not in compliance with the description requirement. Rather, it is an attempt to preempt the future before it has arrived.

In terms of the structural requirements of the nucleic acid molecules in claims 4 and 16, the only difference between the cases reviewed by the court and Board and the subject matter of claims 4 and 16, is that in addition to recitation of a desired protein activity, claims 4 and 16 recite an arbitrary structural relationship between the claimed nucleic acid sequence and the single disclosed species of nucleotide and amino acid sequences based upon hybridization of nucleic acid or % identity to an amino acid sequence. Hybridization of two nucleic acids under high stringency conditions, such as recited in claim 4, part (c), requires only that the two nucleic acids share between 25 and 50 nucleotides in common. See Kennell, Progr. Nucleic Acid Res. Mol. Biol. 11: 259-301, 1971 at the paragraph bridging pages 260-261. Such a sequence encodes only 8-16 amino acids. Consequently, claim 4 embraces nucleic acid molecules encoding polypeptides that could share as few as 8-16 contiguous amino acids in common out of the 950

or 921 amino acids of SEQ ID NO: 18 or 20, respectively. Conversely, a nucleotide sequence that differs in every wobble base from SEQ ID NO: 17, for example, would encode SEQ ID NO: 18, but would not detectably hybridize to SEQ ID NO: 17 under any conditions. Thus, the recited structural relationship is arbitrary since neither the specification nor the prior art discloses any definitive relationship between protein function and % identity or homology at the nucleotide level; and the specification does not describe a single species of nucleic acid that encodes a functional protein that is not either 100% identical to SEQ ID NO: 17 or 19 or that encodes a polypeptide that is not 100% identical to SEQ ID NO: 18 or amino acids 1-921 of SEQ ID NO: 20.

While one of skill in the art can readily envision numerable species of nucleic acid sequences that hybridize to a reference nucleotide sequence under a given set of conditions and that encode a polypeptide at least a given % identity to a recited reference amino acid sequence, one cannot envision which of these also encode a polypeptide with a specified activity. The fact remains that the actual nucleic acid sequences which encode a protein with a particular activity or the actual amino acid sequences of such a protein *cannot* be envisioned any better when the possible choices are narrowed from all possible sequences, to all possible sequences with an arbitrary structural relationship with a known functional sequence. If one skilled in the art were to make a synthetic nucleotide sequence that encoded a polypeptide with 95% identity to the reference amino acid sequence or hybridized to the reference sequence under "stringent conditions", he would be no more able to say whether it encoded a polypeptide with CLR11.3 function than if the nucleotide sequence encoded a polypeptide that was only 10% identical to

the reference polypeptide sequence. Nor would he be able to say whether the sequence existed in nature.

The specification does not provide any information on what amino acid residues are necessary and sufficient for the disclosed activities, much less the undisclosed activities. The specification also provides no teachings on what amino acid sequence modifications, e.g. insertions, deletions and substitutions, would be permissible in a variant polypeptide that would improve or at least would not interfere with the biological activity or structural features necessary for the biological activity and stability of the protein. Since there were no other examples of a functional CLR11.3 protein known that have structural homology with SEQ ID NO: 18 or 20, it is not possible to even guess at the amino acid residues which are critical to its structure or function based on sequence conservation. The comparison of SEQ ID NO: 18 or 20 to the other disclosed CATERPILLER family proteins is no help since it has not been disclosed whether these proteins share an activity, e.g. binding to a specific compound.

Furthermore, it is known in the art that even conservative amino acid substitutions can adversely affect proper folding and biological activity if amino acids that are critical for such functions are substituted, and the relationship between the sequence of a polypeptide and its tertiary structure is neither well understood nor predictable (see Ngo, in The Protein Folding Problem and Tertiary Structure Prediction, Merz et al. (eds.), Birkhauser Boston: Boston, MA, pp. 433 and 492-495, 1994). Rudinger (in Peptide Hormones, Parsons (ed.), University Park Press: Baltimore, MD, pp. 1-7, 1976) discloses that even for peptide hormones, which are much smaller than the instant human CLR11.3 protein, one cannot predict variant amino acid sequences for a biologically active polypeptide. Rather one must engage in "case to case

painstaking experimental study" to determine active variants (see page 7). Consequently, excessive trial and error experimentation would have been required to identify the necessary nucleic acid sequence derivatives encoding a protein with an activity of SEQ ID NO: 18 or 20 with an amino acid sequence differing from SEQ ID NO: 18 or 20 since the amino acid sequence of such polypeptides could not be predicted - even were all the "biological activities normally associated" with CLR11.3 known.

As set forth in *In re Fisher,* 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

In *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 USC 112, 1st para., if only a few of the sequences that meet the functional limitations of the claim are disclosed and if undue experimentation would be required of one skilled in the art for determining other genetic sequences embraced by the claim. This is the case here, where specification discloses only two putative functional amino acid sequences, SEQ ID NO: 18 or 20, for a polypeptide having the necessary activity, and provides no guidance on determining which polypeptide variants of SEQ ID NO: 18 or 20 which would have an activity of SEQ ID NO: 18 or 20.

To put the situation in perspective, the number of possible amino acid sequences of 921 amino acids, as with that of SEQ ID NO: 20, in length is 20^{921} (approx. 10^{1198}). The number of possible nucleotide or amino acid sequences that are of a given %identity relative to a reference sequence, where all differences between the possible sequences and the reference sequence are substitutions, can be calculated by the following expansion formula:

$$N = XL + X^2L(L-1)/2! + X^3L(L-1)(L-2)/3! + \ldots + X^{n-1}L(L-1)(L-2)\ldots(L-(n-2))/(n-1)! +$$

$$X^nL(L-1)(L-2)\ldots(L-(n-1))/n!$$

where N is the number of possible sequences, X is the number of different residues that can be substituted for a residue in the reference sequence, L is the length of the reference sequence, n is the maximum number of residues that can be substituted relative to the reference sequence at a given % identity. For a nucleotide sequence, X is 3 (alternate nucleotides); for an amino acid sequence, X is 19 (alternate amino acids). The n^{th} term of the expansion can be rewritten as:

$$X^n \cdot {}^{L!}/_{(L-n-1)!n!}$$

For a 921 amino acid sequence that is at least 95% identical to a reference sequence of 921 amino acids, e.g. SEQ ID NO: 20, the number of possible sequences having 45 amino acid substitutions relative to the reference (the penultimate term of the formula) is approximately 2.1×10^{137}, whereas the number of possible sequences having 46 amino acid substitutions relative to the reference (the final term of the formula) is approximately 7.7×10^{139}. So the last term is approximately equal to N, i.e. the preceding terms contribute little to the total. Also, as the number of permitted substitutions increases the number of possible variant sequences increases

geometrically. In a genus of polypeptides that are at least 95% identical to a reference, nearly all will be exactly 95% identical.

While limiting the scope of potential sequences to those that are at least 95% identical to a reference, for example, greatly reduces the number of potential sequences to test (10^{1198} vs. 7.7×10^{139}) it does not do so in any meaningful way. The breadth for nucleic acid encoding a functional CLR11.3 and is at least 95% identical to SEQ ID NO: 19 is even more extreme. If all the variant nucleotides occur in wobble positions of different codons, with no more than one per codon, then the amino acid sequence encoded could differ from that of SEQ ID NO: 20 by 15%, i.e. 138 amino acids could differ. The number of potential variants differing from SEQ ID NO: 20 by only substitution in this case would be 6.9×10^{236}. The number of atoms in the universe is estimated to be between 10^{70} and 10^{90}. Even were it possible to convert all the mass of the universe into a collection of nucleic acid molecules each encoding one variant CLR11.3 readable on the claims, one would be able to make and test only an infinitesimal fraction of the variants embraced by the claims.

Therefore, inclusion of the recited structural relationships in claims 4 and 6 also do not distinguish the instant fact situation from those reviewed in *Amgen, Fiers,* and *Regents of the Univ. Calif.* Thus, the instant specification is inadequate to describe and enable how to make the nucleic acid molecules as broadly as they are claimed here.

Applicant's arguments filed 10/26/07 have been fully considered but they are not persuasive. Applicant merely alleges that the claim amendments overcome this rejection, without any explanation of how.

Claim 16 remains rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Applicant's arguments filed 10/26/07 have been fully considered but they are not persuasive. For one to determine the scope of this claim, one first must know what functions of the polypeptide are embraced. That CLR11.3 is involved in a proinflammatory response does not inform one of the function of the polypeptide that leads to its involvement in a proinflammatory response. While one might be able to assay for the ability of a fragment to inhibit expression of NF-κB mediated by MyD88, claim 16 is not limited to fragments with this "function".

Claim Rejections - 35 USC § 102

Claims 4, 16, and 20 remain rejected under 35 U.S.C. 102(b) as being anticipated by Conklin, D.C., WO 01/04307, for the reasons of record set forth in the Office action of 4/23/07.

Applicant's arguments filed 10/26/07 have been fully considered but they are not persuasive. Applicant merely alleges that the claim amendments overcome this rejection, without any explanation of how. The nucleic acid of Conklin comprises a nucleic acid that differs from instant SEQ ID NO: 17 by only four nucleotides and would certainly hybridize to the complement of SEQ ID NO: 17 or 19 or a nucleic acid at least 95% identical to SEQ ID NO: 19.

Claims 55 and 56 have not been included in this rejection solely because there is no evidence of record that CATERPILLER 11.3 inherently has the characteristic of inhibiting NF-κB function. However, should applicant amend claims 55 and 56 to recite inhibition of induction of NF-κB expression, as suggested, they would be subject to the instant rejection.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe, Ph.D. whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, Ph.D. can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Scott D. Priebe

SCOTT D. PRIEBE, PH.D
PRIMARY EXAMINER